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(54) Title: TREATMENT OF LOWER URINARY TRACT SYMPTOMS AND PHARMACEUTICAL COMPOSITIONS FOR USE THEREIN

(57) Abstract: A medical condition in men known as Lower Urinary Tract Symptoms or LUTS is treated by the administration of a muscarinic receptor antagonist in combination with at least one of a 5α-reductase inhibitor and an α-adrenergic receptor blocker.

TITLE OF THE INVENTION
TREATMENT OF LOWER URINARY TRACT SYMPTOMS AND PHARMACEUTICAL COMPOSITIONS FOR USE THEREIN

BACKGROUND OF THE INVENTION

Lower Urinary Tract Symptoms (LUTS) is a well-recognized condition of men which includes some or all of the following: obstructive urinary symptoms such as slow urination; dribbling at the end of a urination; inability to urinate and/or the need to strain to urinate at an acceptable rate or irritative symptoms such as frequency and/or urgency. These irritative symptoms may result from detrusor overactivity secondary to bladder outlet obstruction resulting from prostatic enlargement or proximal urethral smooth muscle hyperreactivity.

Approved therapies for these conditions include treatment with 5α-reductase inhibitors, such as finasteride, (US Patents 4,377,584 and 4,760,071) which shrink the prostate; and α-adrenergic receptor blockers such as terazosin (US Patent 4,026,894) or doxazosin (US Patent 4,188,390) which relax smooth muscle.

Combinations of 5α-reductase inhibitors with α-adrenergic blockers have been described for use in the treatment of benign prostatic hyperplasia (US Patent 5,753,641).

Bladder outlet obstruction may result in detrusor muscle hyperreactivity which may manifest itself as urge/urge incontinence. Muscarinic receptor antagonists, including those with relative specificity for the M3 receptor-subtype can be used to treat urge/urge incontinence.

With this invention there are provided pharmaceutical compositions comprising a muscarinic receptor antagonist and at least one agent of an approved therapeutic class for the treatment of benign prostatic hypertrophy (BPH). The invention is also concerned with methods of treating LUTS with the pharmaceutical compositions and the components thereof.

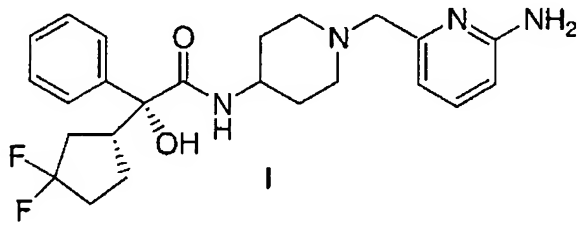
SUMMARY OF THE INVENTION

This invention is concerned with methods of treatment of Lower Urinary Tract Symptoms (LUTS) and pharmaceutical compositions comprising a muscarinic receptor antagonist and at least one other active ingredient selected from a 5α-reductase inhibitor and an α-adrenergic receptor blocker.

DETAILED DESCRIPTION OF THE INVENTION

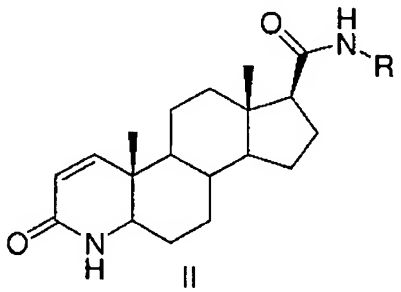
One embodiment of this invention is a pharmaceutical composition comprising an effective amount of a combination of: (a) a muscarinic receptor antagonist; and at least one other active ingredient selected from: (b) a 5α-reductase inhibitor; and (c) an α-adrenergic receptor blocker, in combination with a pharmaceutically acceptable carrier.

The muscarinic receptor antagonists useful in the compositions of this invention include but are not limited to tolterodine, oxybutinin, darifenacin and a compound of structure I and related compounds disclosed and claimed in WO98/05641 (US Patent Application Serial No. 08/903768, filed July 30, 1997) and pharmaceutically acceptable salts thereof.



I

Among the 5α-reductase inhibitor compounds useful in the compositions and methods of the present invention are those of structural formula II (US Patent 4,377,584).



II

wherein R is selected from:

(a) C_{1-10} alkyl, unsubstituted or substituted with one to three halogen substituents, and

(b) phenyl, unsubstituted or substituted with one to three substituents independently selected from halogen, methyl, and trifluoromethyl.

In one embodiment of compounds of structural formula II, R is selected from

(a) unsubstituted C_{1-10} alkyl, and

(b) phenyl unsubstituted or substituted with one or two trifluoromethyl substituents.

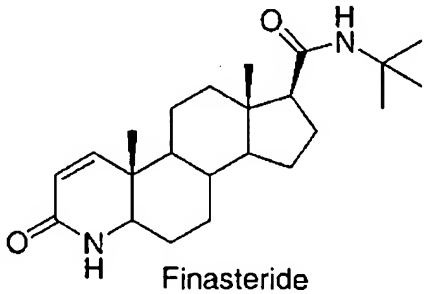
In another embodiment of compounds of structural formula II, R is t-butyl to provide the compound, finasteride.

In yet another embodiment of compounds of structural formula II, R is 2,5-bis(trifluoromethyl)phenyl, to provide the compound, dutasteride (US Patent 5,565,467).

The term "halo" or "halogen" is meant to include fluoro, chloro, bromo and iodo.

The term "C_{1-10} alkyl" is meant to include both straight-and branched-chain alkyl groups of one to ten carbon atoms in length, not limited to: methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl and the isomers thereof such as isopropyl, isobutyl, secbutyl, t-butyl, isopentyl, isohexyl, etc.

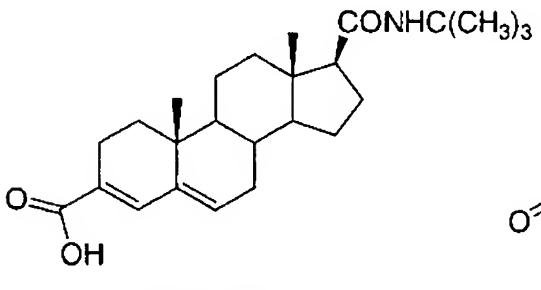
The preferred 5α-reductase inhibitor of the above type is finasteride (shown below) disclosed in US Patent 4,760,071, which is incorporated by reference herein in its entirety.



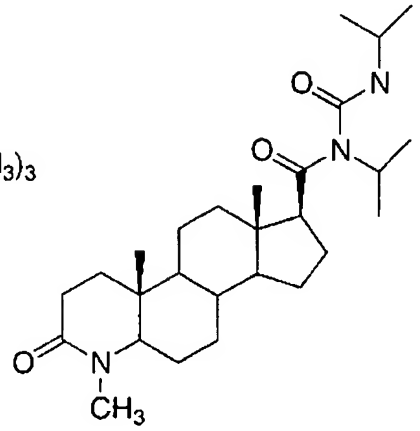
Finasteride

Other inhibitors of 5α-reductase type 2 useful in the methods of the present invention include epristeride (US Patent 5,017,568), turosteride (US Patent

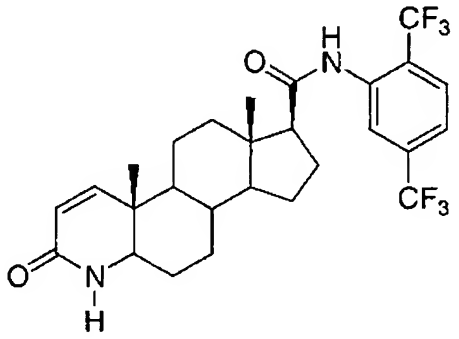
5,155,107) and dutasteride (US Patent 5,565,467) shown below. All three US patents are incorporated by reference herein in their entirety.



epristeride



turosteride



dutasteride

The α-adrenergic receptor blockers useful in the pharmaceutical compositions of this invention include but are not limited to terazosin (US Patent 4,026,894), doxazosin (US Patent 4,188,390), prazosin (US Patent 3,511,836), bunazosin (US Patent 3,920,636), indoramin (US Patent 3,527,761), alfuzosin (US Patent 4,315,007), abanoquil (US Patent 4,686,228), naftopidil (US Patent 3,997,666), phentolamine, tamsulosin (US Patent 4,703,063), trazodone, dapiprazole, phenoxybenzamine, idazoxan (US Patent 4,818,764), efaroxan (US Patent 4,411,908) and yohimbine; and pharmaceutically acceptable salts thereof. The US patents are incorporated by reference herein in their entirety. Preferred α-blockers include but are

not limited to doxazosin, terazosin, and prazosin; and pharmaceutically acceptable salts thereof.

In the pharmaceutical compositions of this invention, each active ingredient is present in an amount that would be present in a formulation comprising it as a sole active ingredient. The muscarinic receptor antagonist is present in an amount ranging from about 0.2 mg to about 20 mg, preferably about 2 mg per dose. The 5α-reductase inhibitor is present in an amount ranging from about 2 mg to about 20 mg, preferably about 5 mg per dose. The α-adrenergic receptor blocker is present in an amount ranging from about 1 mg to about 25 mg, and preferably about 10 mg per dose.

The pharmaceutical compositions containing the active ingredients may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Patents 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed with water or miscible solvents such as

propylene glycol, PEGs and ethanol, or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethycellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example, beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example, liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring

phosphatides, for example, soybean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxy-ethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Cosolvents such as ethanol, propylene glycol or polyethylene glycols may also be used. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The active ingredients may also be administered in the form of a suppository for rectal administration of the drugs. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Another embodiment of this invention is a method of treating Lower Urinary Tract Symptoms (LUTS) comprising the administration of an effective amount of a composition comprising (a) a muscarinic receptor antagonist and at least one member selected from the group consisting of (b) a 5α-reductase inhibitor and (c) an α-adrenergic receptor blocker to a patient in need of such treatment. The active agents for use in the method of treatment of this invention are those described for use in the pharmaceutical formulation.

An "effective amount" as used herein is that amount of the composition that will elicit the biological or medical response being sought. The

daily dose of each of the active agents employed in the method of treatment of this invention is similar to the doses described for use in the pharmaceutical composition. It will be understood, however, that the specific dose level for any particular patient may depend upon a variety of factors including the age, body weight, general health, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The two or three active agents being administered in the method of treatment of this invention can be administered together combined in a single dosage form or they can be administered separately, essentially concurrently, each in its own dosage form but as part of the same therapeutic treatment program or regimen, and it is contemplated that separate administration of each compound, at different times and by different routes, will sometimes be recommended. Thus, the two or three components need not necessarily be administered at the same time. In a preferred embodiment, administration is timed so that the peak pharmacokinetic effect of one component coincides with the peak pharmacokinetic effect for the other component(s).

EXAMPLE 1

Tablet Preparation

Tablets containing 2 mg. of muscarinic receptor antagonist and 5 mg. of 5α-reductase inhibitor are prepared as illustrated below.

Muscarinic antagonist (Structure I)	2 mg.
5α-reductase inhibitor (finasteride)	5 mg.
Microcrystalline cellulose	37.25 mg.
Modified food corn starch	37.25
Magnesium stearate	0.50 gm.

All of the active ingredients. cellulose and a portion of the corn starch are mixed and granulated to 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets.

EXAMPLE 2

Tablet Preparation

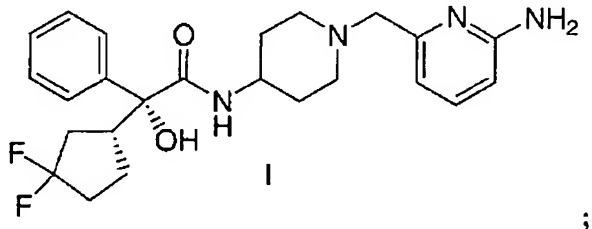
Muscarinic antagonist (Structure I)	2 mg.
5α-reductase inhibitor(finasteride)	5 mg.
α-receptor blocker (doxazosin)	10 mg.
Microcrystalline cellulose	100 mg.
Modified food corn starch	4.25 mg.
Magnesium stearate	0.75 mg.

Tablets are prepared from the above composition by substantially the same procedure as described in Example 1.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for the treatment of Lower Urinary Tract Symptoms (LUTS) comprising an effective amount of a combination of: (a) a muscarinic receptor antagonist and at least one member selected from the group consisting of (b) a 5α-reductase inhibitor and (c) an α-adrenergic receptor antagonist, and a pharmaceutically acceptable carrier.

2. The composition of Claim 1 wherein the muscarinic antagonist (a) is selected from the group consisting of tolterodine, oxybutinin, darifenacin and a compound of structure I



I

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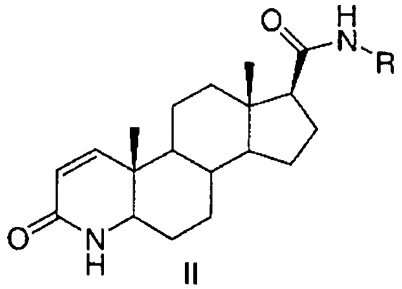
the 5α-reductase inhibitor (b) is selected from the group consisting of epristeride, turasteride and a compound of structural formula II



II

wherein R is selected from:

(a) C_{1-10} alkyl, unsubstituted or substituted with one to three halogen substituents, and

(b) phenyl, unsubstituted or substituted with one to three substituents independently selected from halogen, methyl, and trifluoromethyl; and

the α-adrenergic receptor blocker (c) is selected from the group consisting of terazosin, doxazosin, prazosin, bunazosin, indoramin, alfuzosin, abanoquil, naftopidil, phentolamine, tamsulosin, trazodone, dapiprazole, phenoxybenzamine, idazoxan, efaroxan and yohimbine; and pharmaceutically acceptable salts thereof.

3. The composition of Claim 2 wherein the 5α-reductase inhibitor is the compound of structure II wherein
R is selected from

(a) unsubstituted C_{1-10} alkyl, and

(b) phenyl unsubstituted or substituted with one or two trifluoromethyl substituents.

4. The composition of Claim 3 wherein the 5α-reductase inhibitor is the compound of formula II wherein R is t-butyl (finasteride) or 2,5-bis-(trifluoromethyl)phenyl (dutasteride).

5. The composition of Claim 4 wherein the 5α-reductase inhibitor is finasteride.

6. The composition of Claim 2 wherein the muscarinic receptor antagonist is the compound of structure I, and the α-adrenergic receptor antagonist is a member selected from the group consisting of doxazosin, terazosin and prazosin.

7. The composition of Claim 3 wherein the muscarinic receptor antagonist is the compound of structure I, and the α-adrenergic receptor antagonist is a member selected from the group consisting of doxazosin, terazosin and prazosin.

8. The composition of Claim 4 wherein the muscarinic receptor antagonist is the compound of structure I, and the α-adrenergic receptor antagonist is a member selected from the group consisting of doxazosin, terazosin and prazosin.

9. The composition of Claim 5 wherein the muscarinic receptor antagonist is the compound of structure I, and the α-adrenergic receptor antagonist is a member selected from the group consisting of doxazosin, terazosin and prazosin.

10. The composition of Claim 1 comprising an effective amount of (a) a muscarinic receptor antagonist and (b) a 5α-reductase inhibitor and a pharmaceutically acceptable carrier only.

11. The composition of Claim 2 comprising an effective amount of (a) a muscarinic receptor antagonist and (b) a 5α-reductase inhibitor and a pharmaceutically acceptable carrier only.

12. The composition of Claim 3 comprising an effective amount of (a) a muscarinic receptor antagonist and (b) a 5α-reductase inhibitor and a pharmaceutically acceptable carrier only.

13. The composition of Claim 4 comprising an effective amount of (a) a muscarinic receptor antagonist and (b) a 5α-reductase inhibitor and a pharmaceutically acceptable carrier only.

14. The composition of Claim 5 comprising an effective amount of (a) a muscarinic receptor antagonist and (b) a 5α-reductase inhibitor and a pharmaceutically acceptable carrier only.

15. The composition of Claim 6 comprising an effective amount of (a) a muscarinic receptor antagonist and (c) the α-adrenergic receptor blocker and a pharmaceutically acceptable carrier only.

16. The composition of Claim 7 comprising an effective amount of (a) a muscarinic receptor antagonist and (c) the α-adrenergic receptor blocker and a

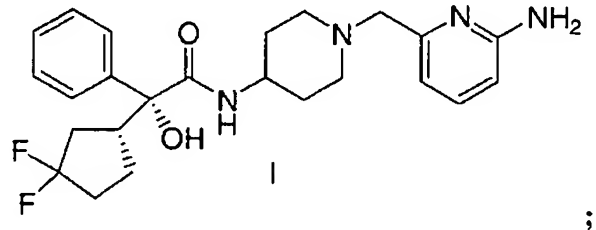
pharmaceutically acceptable carrier only.

17. The composition of Claim 8 comprising an effective amount of (a) a muscarinic receptor antagonist and (c) the α-adrenergic receptor blocker and a pharmaceutically acceptable carrier only.

18. The composition of Claim 9 comprising an effective amount of (a) a muscarinic receptor antagonist and (c) the α-adrenergic receptor blocker and a pharmaceutically acceptable carrier only.

19. A method of treatment of Lower Urinary Tract Symptoms (LUTS) comprising the administration to a patient in need of such treatment of an effective amount of a combination of: (a) a muscarinic receptor antagonist and at least one member selected from the group consisting of (b) a 5α-reductase inhibitor and (c) an α-adrenergic receptor antagonist, and a pharmaceutically acceptable carrier only.

20. The method of Claim 19 wherein the muscarinic antagonist (a) is selected from tolterodine, oxybutinin, darifenacin and a compound of structure I



I

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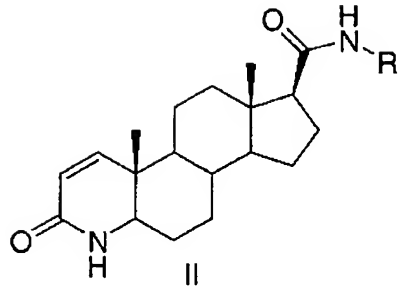
the 5α-reductase (b) is selected from the group consisting of epristeride, turosteride and a compound of structural formula II



II

wherein R is selected from:

(a) C_{1-10} alkyl, unsubstituted or substituted with one to three halogen substituents, and

(b) phenyl, unsubstituted or substituted with one to three substituents independently selected from halogen, methyl, and trifluoromethyl; and the α-adrenergic receptor blocker (c) is selected from terazosin, doxasosin, prazosin, bunazosin, indoramin, alfuzosin, abanoquil, naftopidil, phentolamine, tamsulosin, trazodone, dapiprazole, phenoxybenzamine, idazoxan, efaroxan and yohimbine; and pharmaceutically acceptable salts thereof.

21. The method of Claim 20 wherein the 5α-reductase inhibitor is the compound of structure II wherein
R is selected from

(a) unsubstituted C_{1-10} alkyl, and

(b) phenyl unsubstituted or substituted with one or two trifluoromethyl substituents.

22. The method of Claim 21 wherein the 5α-reductase inhibitor is the compound of formula II wherein R is t-butyl (finasteride) or 2.5-bis-(trifluoromethyl)phenyl (dutasteride).

23. The method of Claim 22 wherein the 5α-reductase inhibitor is finasteride.

24. The method of Claim 23 wherein the muscarinic receptor antagonist is the compound of structure I, and the α-adrenergic receptor antagonist is a member selected from the group consisting of doxazosin, terazosin and prazosin.

25. The method of Claim 24 wherein the muscarinic receptor antagonist is the compound of structure I, and the α-adrenergic receptor antagonist is a member selected from the group consisting of doxazosin, terazosin and prazosin.

26. The method of Claim 25 wherein the muscarinic receptor antagonist is the compound of structure I, and the α-adrenergic receptor antagonist is a member selected from the group consisting of doxazosin, terazosin and prazosin.

27. The method of Claim 26 wherein the muscarinic receptor antagonist is the compound of structure I, and the α-adrenergic receptor antagonist is a member selected from the group consisting of doxazosin, terazosin and prazosin.

28. The method of Claim 19 comprising an effective amount of (a) a muscarinic receptor antagonist and (b) a 5α-reductase inhibitor and a pharmaceutically acceptable carrier only.

29. The method of Claim 20 comprising an effective amount of (a) a muscarinic receptor antagonist and (b) a 5α-reductase inhibitor and a pharmaceutically acceptable carrier only.

30. The method of Claim 21 comprising an effective amount of (a) a muscarinic receptor antagonist and (b) a 5α- reductase inhibitor and a pharmaceutically acceptable carrier only.

31. The method of Claim 22 comprising an effective amount of (a) a muscarinic receptor antagonist and (b) a 5α- reductase inhibitor and a pharmaceutically acceptable carrier only.

32. The method of Claim 23 comprising an effective amount of (a) a muscarinic receptor antagonist and (b) a 5α- reductase inhibitor and a pharmaceutically acceptable carrier only.

33. The method of Claim 19 comprising an effective amount of (a) a muscarinic receptor antagonist and (c) an α-adrenegic receptor blocker and a pharmaceutically acceptable carrier only.

34. The method of Claim 20 comprising an effective amount of (a) a muscarinic receptor antagonist and (c) an α-adrenegic receptor blocker and a pharmaceutically acceptable carrier only.

35. The method of Claim 21 comprising an effective amount of (a) a muscarinic receptor antagonist and (c) an α-adrenegic receptor blocker and a pharmaceutically acceptable carrier only.

36. The method of Claim 22 comprising an effective amount of (a) a muscarinic receptor antagonist and (c) an α-adrenegic receptor blocker and a pharmaceutically acceptable carrier only.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/25534

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/169, 253, 255, 260, 280, 284, 313, 318, 323, 397, 400, 422, 534, 603, 667, 726

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

REGISTRY, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database CAPLUS on STN (Columbus, OH, USA), No. 129:298157, DE MEY, C. ET AL 'A double-blind comparison of terazosin and tamsulosin on their differential effects on ambulatory blood pressure and nocturnal orthostatic stress testing,' abstract, Eur. Urol., 1998, 33(5), 481-488.	1-36
Y	Database CAPLUS on STN, (Columbus, OH, USA), No. 130:32752, DEBRUYNE, F. ET AL. 'Sustained-release alfuzosin, finasteride and the combination of both in the treatment of benign prostatic hyperplasia,' abstract, Eur. Urol., 1998, 34(3), 169-175.	1-36

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 29 NOVEMBER 2000	Date of mailing of the international search report 08 JAN 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer REBECCA COOK Telephone No. (703) 308-1235

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/25534

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database CAPLUS on STN, (Columbus, OH, USA), No. 124:97773, NAKAMURA, K. ET AL. "Percutaneously administrable preparation for treating urination disorder," abstract, WO 9531190 A1, 19951123.	1-36

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/25534

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

A61K 31/13, 31/18, 31/24, 31/33, 31/40, 31/44, 41/47, 31/415, 31/445, 31/495, 31/56, 31/505

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/169, 253, 255, 260, 280, 284, 313, 318, 323, 397, 400, 422, 534, 603, 667, 726